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REMARKS

Support for the Amendments can be found in the original claims and the prior amendments.

For convenience and completeness, pages 2 and following of the Office Action are set forth below in italics, with Applicants' remarks interspersed.

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DETAILED ACTION
Status
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Applicant's reply filed 01/22/2008 is acknowledged. Claims 1-24 are pending.
The objection to claim 9 made in the Office action dated 09/19/2007 is withdrawn in view of Applicant's amendment.
The rejection of claims 3-6,8-10, 12 and 19-22 under 35 U.S.C. 112, 2nd paragraph, made in OA 09/19/2007, are withdrawn in view of Applicant's amendments.
The rejection of claims 1-4,6-8,10,14 and 16 under 35 U.S.C. 102(b) over Verdine et al (WO 98/00435) is withdrawn in view of Applicant's amendment to claim 1 Verdine does not teach exposure of purine bases by a process selected from thermal denaturation/renaturation, alkaline denaturation, or restriction enzyme digestion yielding single-stranded overhangs. Rather, Verdine uses chemical denaturation (i.e treatment with guanidinium-HCl, a chaotropic agent).
The rejection of claims 1,2,5,7,8 and 19 under 35 U.S.C. 102(b) over Heisler et al (US Pat 5,843,654) is withdrawn in view of Applicant's amendment to claim 1. Heisler does not teach exposure of purine bases. Rather, Heisler's affinity handle is histidine residues incorporated in a protein.
The rejection of claims 1-4, 7, 9-12, 16 and 20-22 under 35 U.S.C. 102(b) over Pham et al (BioTechniques 20(3):492-497 (1996)) is withdrawn in view of Applicant's amendment to claim 1, which now recites" 'affinity handles' from shielded purine base sites".
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The Examiner is thanked for the withdrawal of the above 35 USC 112 rejections.

The rejection of claims 1-4, 6, 14-17,23 and 24 under 35 U.S.C. 102(e) over Willson et al (US 2004/0152076) and 35 U.S.C. 102(a) over Murphy et al (WO 02/46398) are maintained as still applicable to the amended claims and as further explained below.
New Rejections
Claim Rejections - 35 USC § 112,2nd paragraph
The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are multiple issues under this section:
With regard to claim 1 ...
1. The phrase "exposure, enhancement, or stabilization of structural "affinity handles" from shielded purine base sites previously present" is vague and indefinite. Does this mean the "affinity handles" consist of or comprise shielded purine base sites? And if the purine base sites are "shielded", are they "affinity handles" in that state? Or must

they first be "un-shielded" (e.g. by "exposure")? Furthermore, the examiner was unable to find any use of the term "shielded purine base" in the original disclosure (hence the NEW MATTER rejection below). See below for recommended language.
For purposes of examination over the prior art, the examiner will interpret this language to mean that the "affinity handles" comprise purine bases, which were "shielded" (i.e involved in base pairs with complementary bases) but have been "un-shielded" by
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selective thermal denaturation/renaturation, alkaline denaturation, or use of restriction enzymes yielding single-stranded overhangs.
2. In the phrase "selectively to either the desired or undesired moieties or nucleic acid", the word "selectively" is unnecessary. Furthermore, the word "to" does not make sense in the context of the claim as amended. Previously, the claim recited, as an option, "introduction" of structural affinity handles, and here the word "to" would make sense. However, since the claim now recites only "exposure, enhancement, or stabilization", the word "to" should become "in" or "within". One could expose, enhance or stabilize structural affinity handles within either the desired or undesired moieties or nucleic acid. See below for recommended language.

Since all other claims depend directly or indirectly from claim 1, they are rejected for the same reasons.
The following language for claim 1 is recommended as a guideline:
A scalable process for the highly selective, high yield separation of a desired product, which may be a nucleic acid or a non-nucleic acid product, from undesired nucleic acid, comprising:
exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid by a process selected from the group consisting of selective thermal denaturation and renaturation, alkaline denaturation, and restriction enzyme digestion yielding single-stranded overhangs;
capture of the desired nucleic acid product or undesired nucleic acid by a technique selective for the exposed purine bases;
and separation of the desired product from the undesired nucleic acid.
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Note the above language is not being recommended for the purpose of
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patentability over the prior art, but merely to overcome the issues under the 35 U.S.C. 112, 2nd paragraph rejection discussed above. Furthermore, should Applicant decide to adopt this suggested language, or otherwise amend claim 1, Applicant should carefully review the depending claims to ensure they are consistent with claim 1 to avoid further rejections under 112, 2nd paragraph.

The Examiner is especially thanked for the helpful suggested wording for Claim 1, which has been amended to conform to that suggestion. Applicant has also reviewed the dependent claims and modified them to conform to the amended Claim 1.

With regard to claims 7 and 10, these claims depend from claim 1 and further recite "introducing" the handles. However, claim 1 has been amended to remove the option of "introducing" the handles, and furthermore requires the handles to comprise purine base sites "previously present". It is unclear how the handles can be required to be both "introduced" and "previously present". This creates a paradox which prevents any meaningful interpretation of claims 7 and 10 for examination over the prior art.
Therefore, claims 7 and 10 will not be further examined.

The Examiner is especially thanked for his helpful suggestion of revised wording for Claim 1 and Claims 7 and 10 have been amended to conform to amended

Claim 1.

Claim Rejections - 35 USC § 112, 1st paragraph
The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to
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one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.
Claim 1 has been amended to recite the term "shielded purine base sites". The examiner was unable to find such a term in the disclosure as filed. While there is support for denaturing double-stranded nucleic acid to expose purine bases, and purine bases in a double-stranded nucleic acid could be regarded as "shielded" in this sense, the term "shielded purine base sites" is broader than this particular embodiment. For example, the term "shielded purine base sites" would encompass purine bases modified with a cleavable "caging" or "blocking" group.
Since all other claims depend directly or indirectly from claim 1, they are rejected for the same reasons.

It is believed that the adoption of the Examiner's suggested language has obviated this objection.

Previous Rejections
Claim Rejections - 35 USC § 102
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless -
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351 (a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21 (2) of such treaty in the English language
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Claims 1-4, 6,14-17,23 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Willson et al (US 2004/0152076) or alternatively under 35 U.S.C. 102(a) as being anticipated by Murphy et al (WO 02/46398). As the disclosures of these references are identical, reference will only be made to teachings in US 2004/0152076.
With regard to claim 1, Willson teaches exposing structural affinity handles from shielded purine base sites previously present by process of selective thermal denaturation and renaturation, thereby inherently producing "non-shielded" purines, followed by capture of the non-shielded purines by IMAC; see paragraphs [0072] and [0110]. Willson also teaches exposing such affinity handles by producing alkaline cell lysates, thus inherently

producing alkaline denatured nucleic acid, followed by capture of such denatured nucleic acid on IMAC columns (see paragraphs [0187]-[0190]).
With regard to claims 2 and 4, Willson introduces single-strandedness into the molecules to be captured by either thermal or alkaline denaturation, as discussed for claim 1.
With regard to claim 3, in the example taught by Willson for clarifying a plasmid lysate (paragraphs [0187]-[0190]), a plasmid preparation is sensitive to host genomic DNA contamination.
With regard to claim 6, Willson teaches IMAC (paragraph [0120]).
With regard to claim 14, Willson teaches IMAC (paragraph [0120]), which comprises adsorption on chelated metal (paragraph [0007]). Application/Control Number: 10/737,403 Art Unit: 1637
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With regard to claims 15,16,17, Willson teaches multi-channel plates ("well plate"), spin columns and magnetic particles (page 5, Table A, Parameter: Support Shape).
With regard to claim 23, Willson teaches HIC (hydrophobic interaction chromatography; page 5, Table A, last 3 lines under heading "Preferred").
With regard to claim 24, Willson teaches RPC (reverse phase chromatography: "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 6, Table A, line 2 under heading "Preferred").

The rejection under 35 USC 102 requires that every feature of the claimed invention be disclosed in the single reference. See e.g. *Structural Rubber v. Park Rubber*, 223 USPQ 1264 (Fed. Cir 1984): "Anticipation is not shown even if...the differences between the claims and the prior art are "insubstantial" and the missing elements could be supplied by the knowledge of one skilled in the art."

The Murphy reference discloses:

"(57) Abstract: An immobilized metal affinity chromatography (IMAC) apparatus and method for separating and/or purifying compounds containing a non-shielded purine or pyrimidine moiety or group such as a nucleic acid, presumably through interaction with the abundant aromatic nitrogen atoms in the purine or pyrimidine moiety. The apparatus and method can also be used to purify compounds containing purine or pyrimidine moieties where the purine and pyrimidine moieties are shielded from interaction with an IMAC ligand from compounds containing a non-shielded purine or pyrimidine moiety or group."

Applicants' Claim 1 reads: A scalable process for the highly selective, high yield separation of a desired product, which may be a nucleic acid or a non-nucleic acid product, from undesired nucleic acid, comprising:

exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid by a process selected from the group consisting of selective thermal denaturation and renaturation, alkaline denaturation, and restriction enzyme digestion yielding single-stranded overhangs;

capture of the desired nucleic acid product or undesired nucleic acid by a technique selective for the exposed purine bases; and

separation of the desired product from the undesired nucleic acid.

Thus, the concept of deliberately and selectively exposing purine bases within the desired (or undesired) molecule to provide handles for its separation is novel and is not disclosed in the Murphy reference.

> *Claim Rejections - 35 USC § 103*
> *The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:*
> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*
> *This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)*
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The inventorship remains the same and the various claimed inventions were commonly owned ever since filing of the Application.

> *Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Willson et al (US 2004/0152076) or Murphy et al (WO 02/46398) in view of Hawkins (US 5,898,071).*
> *The teachings of Willson and Murphy have been discussed. Neither of these references teaches processing multiple samples in parallel.*
> *Hawkins teaches methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60).*
> *It would have been prima facie obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method of either Willson or Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.*

Hawkins only adds microtiter plates and does not render the claimed invention obvious within the meaning of 35 USC 103(a).

The Murphy (Willson) reference relates to metal affinity separation of nucleic acids based on the presence of *existing* structural features and does not teach selective denaturation of desireds or undesireds prior to binding ("capture"). That is, the reference does not teach a major feature of the present invention: "exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid by a process selected from the group consisting of selective thermal denaturation and renaturation, alkaline denaturation, and restriction enzyme digestion yielding single-stranded overhangs;" as recited in Applicants' Claim 1. [Emphasis added.]

This feature was not obvious to Professor Willson, the lead inventor, a person well skilled in the Art [e.g. former Chairman of the Biochemistry Division of the American Chemical Society] at the time the invention claimed in the Murphy (Willson) reference was made. The present application teaches for the first time, the powerful nucleic acid separation technique set forth in Claim 1.

As is pointed out on page 3, paragraph 6 of the present Application, the Murphy (Willson) reference was published prior to the 16 December 2003 filing date of the present application and prior to the Priority Date of the provisional application 60/434,901 filed 20 December 2002.

As stated in the Application at page 4 line 14-16: "None of the above references is understood to teach the steps of introducing affinity handles [exposing purine bases] into certain desired (or undesired) moieties, then using these handles to separate out desired (or undesired) moieties."

In summary, the present invention achieves remarkably advantageous results e.g. excellent separation of plasmid DNA from genomic DNA routinely present in

bacterial cell lysates. This valuable new separation does not work with IMAC without the "handle"-creating purine base exposure step recited in every claim. The separation is difficult or impossible to accomplish by any prior known method. Murphy does not disclose the invention and would surely have done so if the invention were obvious to a skilled person reading Murphy.

> *Response to Arguments*
> *Applicant's arguments filed 01/22/2008 have been fully considered but they are not persuasive.*
> *With regard to the rejection under 35 U.S.C. 102(a) and (e). Applicant argues that the embodiment cited by the examiner, where a deoxyribose tail is introduced as an affinity handle, does not apply to the amended claims. That is, the introduction of such a tag does not involve exposure, enhancement or stabilization of an affinity handle comprising previously present purine bases by a process of selective thermal denaturation and renaturation, alkaline denaturation or the use of restriction enzymes (pages 12-15 of the response).*
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> *This argument is not persuasive, as Willson teaches other embodiments, as discussed in the rejection, which meet the limitations of the amended claims*

Referring to Claim 1 as now presented, Murphy does not disclose the step of "*exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid*" – a major feature of the invention.

The present invention achieves excellent separation e.g. of plasmid DNA from the genomic DNA routinely present in bacterial cell lysates. This separation is inoperative with IMAC without the invention's purine base exposure (handle-creating) separation/denaturation step, recited in each claim. It is difficult or impossible to accomplish such separation by any previously known method. The ability of the claimed invention to readily accomplish this and other valuable often-needed separations (as proven by the date in the Examples in this application) is itself an Unexpected Result. [See e.g. *In re Soni*, 54 Fed.3d 746, 34 USPQ2d 1684, 1687 (Fed. Cir 1986) and 37 CFR § 1.132; Practice I. Unexpected results – MPEP 716.02(a)-(g).]

> *Conclusion*
> *Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37CFR 1.136(a).*

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272 1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300

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scw

/GARY BENZION/

Supervisory Patent Examiner, Art Unit 1637

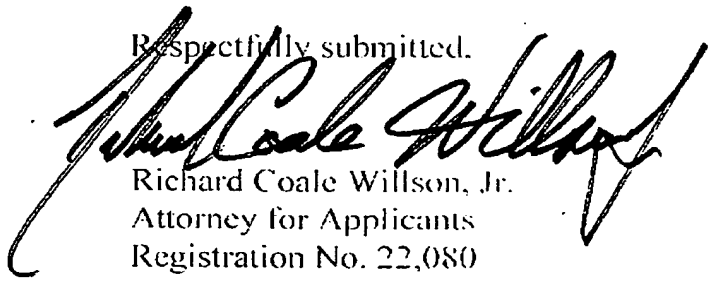
The Amendments are for clarity and are not required to distinguish from the references. No new matter or estoppel is involved.

Any necessary fees (small entity) may be charged to Deposit Account 200336 of Technology Licensing Co. LLC.

This response is being filed within two months of the mailing of the Official Action.

The Examiner is especially invited to indicate some allowable matter, and to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,



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